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Defining Life or Bringing Biology to Life

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Abstract In the present, post-genomic times, systemic or holistic approaches to living phenomena are compulsory to overcome the limits of traditional strategies, such as the methodological reductionism of molecular biology. In this paper, we propose that theoretical and philosophical efforts to define life also contribute to those integrative approaches, providing a global theoretical framework that may help to deal with or interpret the huge amount of data being collected by current high-throughput technologies, in this so-called 'omics' revolution. We claim that two fundamental notions can capture the core of the living, *(basic) autonomy* and *open-ended evolution*, and that only the complementary combination of these two theoretical constructs offers an adequate solution to the problem of defining the nature of life in specific enough—but also encompassing enough—terms. This tentative solution should also illuminate, in its most elementary version, the leading steps towards living beings on Earth.

Keywords Basic autonomy · Open-ended evolution · Life definition · Systems biology · Origin of life

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Introduction

As part of the living world, we naturally have an intuitive grasp on life. Such a primordial or inherent intuition usually tells us that living beings share some property, some basic dynamic attribute that is responsible for their forms and functions, that brings forward their robustness, their responsiveness or their capacity for growth and reproduction… Aristotle was the first philosopher that developed a rational concept of life, which he based on the abstract idea of an animated or active "form". But this unified idea of the living was almost forgotten, in favour of a view of nature as three separated "kingdoms" (mineral, vegetable and animal), where the distinctive character and commonalities of all biological entities were partly lost. The achievement of a new unified concept of life, which encompassed a whole phenomenological world, separate from physical and chemical systems, required a long process of both theoretical and empirical research. In fact, the interpretation of life as a unitary phenomenon, as a common quality or type of organization that could group together a vast domain of natural systems is relatively modern.

Life, in this sense, can be regarded as ≪an invention of the 18th century≫, like philosopher and historian Foucault (1966) said; an invention consolidated during the 19th century, thanks to the development of microscopy and the experimental (chemistry-based) techniques that allowed the detection of some of the material and organizational features shared by such a variety of systems. This unitary conception, of course, received further support from evolutionary theories, which—also during the 19th century—provided evidence of the fact that all present organisms come from a common ancestor. The disproval of spontaneous generation of microorganisms in extant conditions and the Darwinian principle of divergence consolidated the picture of all living beings belonging to a huge family (historically related in a tree-like structure) since Haeckel's time.

Nevertheless, even if it was the combination of results coming from experimental and evolutionary approaches in the—then emerging—field of biology what made possible to establish a first unitary notion of the living (as a separated domain with regard to the non-living world), each of those two approaches put forward a rather different way of conceiving the living phenomenon. They were actually representatives of two alternative traditions or methodologies of work in the general practice of biology: on the one hand, the physiological approach, focusing on how material parts can put and keep together an organism; and, on the other hand, the natural history approach, looking into shared morphologies or adaptations that phylogenetically connect the organisms. In terms of Mayr (1982), the first would be a biology of 'proximate causes' (functional biology) whereas the second (evolutionary biology) would deal with 'ultimate causes'. Two of the major achievements in 20th century biology, the modern synthesis and the discovery of the fundamental molecular mechanisms responsible for the functioning of any living cell, corroborate the validity of that general portray up to our days.

Often we do not realize to what an extent our present view of life reflects an implicit cut, linked to this dual tradition in biology. But, in fact, living systems tend to be regarded from two distinct perspectives (Maynard Smith 1986): (i) as individual organisms in a continuous self-producing activity (metabolism) and in continuous interaction with their respective environments, including other organisms; and (ii) as populations, species or ecosystems following longer-term evolutionary pathways, making up different branches of the whole tree of life (the biosphere: past, present and future).

Our more 'spontaneous' view is certainly the first, because we regularly observe other systems, like us, acting, reacting, behaving in—more or less—unexpected ways, struggling for survival, dying, etc. under different environmental conditions. And we can extrapolate this to other cases, like microorganisms, further away from our personal experience, but which also hold together and respond—more or less—coherently to external stimuli. The second, instead, is more of a culturally—or scientifically-inherited conception: we have *become used to* interpreting life as a result of evolution (rather than the contrary). Dobzhansky's (1973) celebrated sentence ≪nothing makes sense in biology except in the light of evolution≫ is a good example to illustrate how far we see into living beings, now, through a scientific background that provides us with a more global and elaborate perspective, in which the features and behavior of individual organisms gain much deeper meaning. Thus, even though most of what we can directly *observe* in biology is still provided by living individual entities, what we *comprehend* involves other abstract categories that go beyond the time and space occupied by single organisms (e.g. genomes, phylogenetic histories, fitness landscapes, evolving ecologies, and so on), and has enabled a richer re-interpretation of our spontaneous conception.

Nevertheless, that primary tension between the physiological and evolutionary views remains there: who dares to say, at the beginning of the 21st century, that it has been resolved? Quite the contrary, it might be increasing right now. Modern biology was constructed on concepts like species, population, gene, adaptation, etc. (Keller 2000), supposed to be scientifically more sound or rigorous than the idea of organism, or functionally organized system (which had virtually disappeared from biological theory (Morange 2003)). However, by themselves, those apparently more scientific concepts have not carried enough explanatory power, at least under the strict light of molecular-reductionist approaches. As a result, we are witnessing (Etxeberria and Umerez 2006) a return to more holistic/organicist positions (like before molecular biology's revolution, with authors like Woodger, Needham, Waddington or Bertanlanffy),[1] but with more operational power this time.[2]

In this new context, where more and more scientists are becoming aware of the limits of traditional strategies in biology (*Science* special issue on systems biology 2002; Westerhoff and Palsson 2004; Moya et al. 2009), integration seems to be the key word. Integration both (i) as the necessary complement of analytic/decompositional (molecular-reductionist) methods and (ii) as the most adequate approach to reconcile different conceptions of the living and construct a new theoretical framework in which the tension between them is well-channeled: that is, productive. The aim of this paper is to show how efforts to define life may contribute to such an enterprise, somehow giving cohesion or bringing biological sciences together.

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[1] Actually, this new enthusiasm for a systemic view of life has even older roots. Around the end of the 18th century, Kant argued that an organism is a system comprised of a whole and parts, where the whole is the product of the parts, but the parts, in turn, depend upon the whole for their own proper functioning and existence. He understood a mechanism as an operational unit in which the parts exist for one another in the performance of a particular function (what today might be called the "working principles" of a machine). Instead, an organism would be a functional and a structural unity in which the parts exist for and by means of one another in the expression of a particular entity (or identity). Thus, the emergence of parts in an organism is a result of internal interactions, rather than the assembly of preexisting parts, as in a mechanism or in a machine.

[2] Operational power in terms of new methodologies of work (combining *in silico* and *in vitro* strategies) that make possible to study complex holistic systems, like living systems, in radically novel ways (Moreno et al. 2010). This is, in fact, reflected in the (re-)emergence of new research fields, like systems biology (Serrano 2007) or synthetic biology (Peretó and Català 2007).

Grasping the Core of Life: Autonomy in Evolution

If we accept that biology is at a historical crossroads, perhaps it would be wiser to keep a cautious attitude, wait for events and advances to happen, and in some ten or twenty years, once the synthetic approaches have delivered their first full results, or an extraterrestrial mission has found proof of alternative living forms, come back to the question of the nature of life. Actually, there are several good reasons (Cleland and Chyba 2002, 2007), to believe that things might not be ripe enough to try to enwrap life into a definition. In particular, we lack examples of life that do not depend on—or are not directly related with—life as we know it on planet Earth. Therefore, we cannot be sure to what extent ours is a representative case, and it will remain difficult to know with certainty how a general theory of biological phenomena should be constructed until those different examples (at least one) are synthesized in the lab or found elsewhere in the universe.

Having said that, we consider that the present situation in biology is not at all like the one (in 17th century chemistry) of trying to define—or find the true nature of—water when the molecular theory of matter had not yet been developed (Cleland and Chyba 2002). The amount of accurate scientific data and knowledge about living systems available these days is enormous. So much so that it is becoming really hard to assimilate. Of course, the discovery of some system or phenomenon that we unanimously agree to regard as an alternative form of life, when it comes (if it eventually comes), will have deep implications and change profoundly our worldviews and our conception of the living. But, meanwhile, efforts to put together explicitly, in a distilled way, what our day-to-day increasing biological knowledge is telling us about the actual concept of life should not be abandoned. Quite the contrary, they should be encouraged, as part of what biology is really lacking right now: more encompassing approaches that contribute to integrate the huge amounts of data and relevant information being continuously generated.

As we have argued in more detail elsewhere (Ruiz-Mirazo et al. 2004; Ruiz-Mirazo and Moreno 2010), current scientific knowledge gathered from the diversity of living entities on Earth, and the diversity of investigations carried out on them, enables us to start discerning what is necessary and what is contingent in their organization and, in that way, achieve eventually a more complete or congruent characterization of the phenomenon of life, in its minimal general sense.

From our perspective, the key concepts to grasp the fundamental core of the living phenomenon are 'basic autonomy' (Ruiz-Mirazo and Moreno 2004; Ruiz-Mirazo et al. 2004) and 'open-ended evolution' (Ruiz-Mirazo et al. 2004, 2008). Autonomy, in this minimal (bio-)chemical sense, covers the main properties shown by any living system at the individual level: (i) self-construction (i.e., the fact that life is continuously building, through cellular *metabolisms*, the components which are directly responsible for its behaviour) and (ii) functional action on/through the environment (i.e., the fact that organisms are *agents* that necessarily modify their boundary conditions in order to ensure their own maintenance as far-from-equilibrium, dissipative systems). Open-ended evolution, in turn, covers the properties of life as a collective-historical phenomenon, i.e., as an intricate network of interacting individuals (organisms), bringing about other similar individuals, and undergoing a long-term process of change which allows for an indefinite increase in their complexity (always under the constraints given by a finite physical-chemical world). But, more importantly, according to the way we define and use these concepts, a process of open-ended evolution could not occur except in the context of a population of autonomous systems; and, conversely, the unfolding of autonomous systems and their long-term maintenance depends on the fact that they get inserted in an open-ended evolutionary route.

Therefore, this general conception somehow tries to bring together the main results and theoretical legacy of those two traditions in biology to which we were referring previously. On those lines, life would be (Ruiz-Mirazo and Moreno 2010) ≪a *complex network of self-reproducing* autonomous *agents whose basic organization is instructed by material records generated through the* open-ended*, historical process in which that collective network evolves*≫, which comes basically from the realization that collective-evolutionary and individual-systemic aspects of the living are so deeply intertwined that cannot be set apart. Any living being that we know (so far) cannot exist but in the context of a global network of similar systems. This is clearly reflected in the fact that genetic components (which specify the metabolic machinery and organization of single biological entities), in order to be functional, have to be shaped through a process that involves a great amount of individual systems and also many consecutive generations, or reproductive steps.

Someone would object that this is an Earth-chauvinist conception, not audacious enough as a generalized or universal notion of the living. However, even if the concrete evolutionary pathway followed by biological systems on our planet were unique and full of contingent aspects, the *type* of evolutionary process that living organisms are engaged in (i.e., open-ended evolution) results from a set of general conditions with far-reaching consequences. In particular, as explained a bit further below, we claim that those conditions could actually be crucial for the robust, long-term sustainability of any living phenomenon as a whole (i.e., of any biosphere).

As argued in a previous paper (Ruiz-Mirazo et al. 2004), in comparative terms, our proposal is more restrictive, more demanding than the standard conception/definition of life (Joyce 1994): 'autonomy' in that sense requires—and provides—more than the bare 'self-maintenance' of a chemical network (especially when that self-maintenance is understood as the direct consequence of a molecular genetic program: see Luisi's (1998) criticism). Equally, the definition above leads to specific requirements for candidate systems that go beyond those coming from the autopoietic (Varela et al. 1974) or the chemoton criteria (Gánti 1975), for instance.

Furthermore, our definition also comprises a particular hypothesis to tackle the problem of the origins of living systems. There is no space here to go into a detailed account of it but, according to our general scheme, between chemical autocatalytic networks and full-fledged biological cells, a series of complex transitions in suprachemical but still 'infrabiological' systems (Szathmáry's *sensu*), both at the level of individual autonomous systems (from 'basic' to 'hereditary' autonomous systems) and at the level of their collective interactions (competitive/selective dynamics, primary food/recycling-webs, ecopoiesis), have to take place. The highly sophisticated molecular and organizational constraints required to implement genetic mechanisms (necessary for a fully open-ended evolution) would make these more plausible in the latest stages of the origins of life, whereas autonomous cellular systems (which would solve other crucial problems, like the control on matter-energy resources necessary to keep a far-from-equilibrium component-production system running) would play the bridging role. As conceptually proposed by Oparin (1924), the complete scheme of those transitions under primitive Earth conditions and the explanation on the articulation of the suprachemical/infrabiological subsystems (e.g. templates, boundaries, catalytic networks), would represent a first step towards a coherent narrative on the origin of life.

On the Importance of the Evolutionary Dimension

Therefore, during the process of life emergence, proto-metabolic autonomous systems would generate mechanisms that make possible the articulation of a network of systems beyond the ontogenic, individual organization and particular histories of each of them. This also involves radical changes in the way those proto-metabolisms are run, going from coupled autocatalytic cycles (probably already self-enclosed in a vesicle) to genetically-instructed, enzymatic pathways, interconnected and regulated in complex ways, within a cellular organization that controls very efficiently the flow of matter and energy through it. But, more importantly, it involves some reliable way to keep and transmit the complexity generated on the way (i.e., hereditary/reproductive mechanisms) so that the resulting population of systems can undergo, overall, a process of indefinite production (and, thus, potential increase) of complexity—throughout the onset of natural selection (de Duve 2005a,b).

The evolutionary dimension, then, brings with it a different, longer-term, time scale (a history beyond a particular organism's lifetime) and a different, much wider space scale (collections of similar, geographically spread systems, reproducing and—sooner or later—competing for limited resources: i.e., ecosystems), but has also crucial implications at the individual level, because it is a very special type of metabolic organization (what we call 'genetically-instructed metabolism') that can sustain all this. Of course, evolutionary aspects have to be regarded as 'capacities' in so far as concrete individual organisms are concerned. Gánti (1987) was very aware of this and that is why he proposed the distinction between 'absolute or actual' life criteria and 'potential' life criteria. The former apply to ≪every living being at every moment of its life without exception≫; and the latter, ≪not being necessary criteria for the living state of the individual organisms, are indispensable with regard to the surviving of the living world≫ (Gánti 1987, p. 68–69).[3] And such a distinction also helps to overcome problems posed to life definitions by certain borderline cases (e.g.: resting seeds, a frozen tissue culture, sterile animals, etc.).

However, it should not be forgotten that evolution constitutes not only a capacity or a process of change but comprises a real complex collective network at work. Evolution is ≪the derivational history of organism-environment complexes≫, as Oyama (2002) has nicely expressed. In other words, organisms develop a complex biophysical environment around them that, in turn, plays a fundamental role in their individual development. As recently pointed out by Dupré and O'Malley (2009), life is the consequence of the intersection of lineage (evolution) and metabolism (individuals), and cooperation is as important as competition in the constitution of living matter. So we find here two entangled processes, happening at different rates and locations, but mutually dependent, since neither can be actually understood without referring to the other.

Therefore, it is the progressive construction of a complex meta—or supra-systemic organization what explains the creative potential of evolution. In contrast with the apparent fragility/instability of complex physico-chemical systems, life is able to steadily maintain much higher levels of structural and relational complexity. And this is achieved through the ongoing triggering of trans-generational changes in the organization of its individuals and their effects, as agents, on the environment. Actually, if it were not for the invention of evolution, nature most probably would not be able to overcome a preliminary threshold of complexity, below which—as von Neumann (1949) already anticipated—that complexity could not maintain itself or thrive. At a certain point in the process of origins of life evolution becomes, somehow, intrinsic to it: like a cyclist that can only keep the balance by pedaling,

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[3] Among the absolute life criteria Gánti includes: inherent unity and stability, metabolism, information-carrying subsystem and program control; and the potential criteria would be: growth and reproduction, capability of hereditary change and evolution, mortality.

life maintains itself, in the long run,[4] by its own evolving. As a result, biological systems, in that 'minimal core' sense, apart from being much more complex than inert systems, hold the potential—not the tendency, but the potential—to become ever more complex.

In those lines, it is quite remarkable that, starting from the first modes of selective evolution dynamics in the most simple 'proto-organisms', through the invention of systems with reliable heredity (hypothetical RNA world), origins of translation and genetic code (DNA-RNA-protein world), post-transcriptional editing processes, symbiosis, sex, development, and so on, the mechanisms of evolution have themselves evolved.[5] In other words, the genesis, through evolution, of new forms of organism and collective (meta-individual) organization has modified, in turn, the strategies of evolution. For sure, evolutionary changes do not just result from the operation of novel mechanisms, but also from the use of former ones, which are almost never completely erased. As a matter of fact, in the history of life that we know, increasingly complex organism types have developed by means of conserving and building upon the previous, simpler ones—i.e., through a process of 'tinkering' and making use of different functional-hereditary mechanisms. Nevertheless, the new evolutionary pathways tried by complex organisms are often "orthogonal" or incommensurable with regard to the old ones. So, even if there is a basic set of common mechanisms working along the whole evolutionary history of life on Earth, evolution is, itself, a process in evolution. This is the idea behind the notion of 'evolvability' (Conrad 1979; Kirschner and Gerhart 1998).

Consequently, when the problem of evolution is brought to the fore nowadays, it is quite different from what biologists had in mind a century ago. The main challenges faced these days are: (i) to determine additional evolutionary mechanisms, complementary (or perhaps, in some situations, alternative) to natural selection, showing what could be their relationship with the latter; and (ii) to understand the way in which main evolutionary transitions occur, i.e., precisely, to find out how the process of evolution itself changes in time. Nothing much, so far, is well-established about these issues, but, as we try to explain in the next section, autonomy is surely involved in both.

On the Importance of the Individual Dimension

Natural selection, genetic drift, gene flow, etc., the traditional mechanisms by which population genetics and evolutionary theory in general, up to date, have provided explanations for the great diversity of living forms on Earth, do not seem to be enough to account for many of their complex structural and dynamic features. Different authors, from different perspectives, have made this pretty clear over the years (D'Arcy Thomson 1992 [1917]; Wimsatt 1980; Buss 1987; Kauffman 1993; Salthe 1993; Goodwin 1994; Weber and Depew 1996; Gould 2002). Most of this critical work, together with recent advances in the field of 'evo-devo' (Raff 1996; Laubichler and Maienschein 2007), points

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[4] For shorter-term, individual system maintenance can be ensured through other strategies, more related to the question of autonomy (see next section).

[5] It is now widely accepted that the mechanisms of evolution (especially as far as phenotypic variation or plasticity is concerned, i.e., adaptability, generation of new functionalities, etc.) have themselves evolved (Conrad 1979; Wagner and Altenberg 1996; Kirschner and Gerhart 1998). The reason for these evolutionary changes seems to be the robustness and flexibility of the processes involved, which make them particularly suitable for complex development and physiology.

in the direction that evolutionary theory, in order to be fully explanatory, needs to merge, in a sort of 'new synthesis', with a theory of the organization of individual organisms.[6]

Traditionally, the phenomenological level of organisms had been privileged by evolutionary theory itself, as it was considered that they were the actual units of selection. The reasoning behind was that, in order for natural selection to be applicable there had to be reproducing entities with a high enough cohesion or functional integration, so that the effects of their interactions with the environment and mutual competition for resources determined the survival of each of them, separately taken. However, in more recent years, that classical view was strongly challenged by authors claiming that natural selection could be also working at other levels: e.g., below, at the level of biomolecules (the gene, in particular, Williams 1966; Dawkins 1976), or above, at the level of groups or species (Wynne-Edwards 1986; Gould and Eldredge 1988). In any case, the general outcome of that debate was the overall acceptance (except for the always present radical voices) that natural selection could be acting, in parallel, at multiple levels of the biological hierarchy (Brandon and Burian 1984; Sober and Wilson 1994)

Nevertheless, the question of whether organisms deserve a special place in biological theory is not confined to the problem of units of selection (Ruiz-Mirazo et al. 2000). Instead, we claim that the more significant connection between the idea of organism and its evolutionary dimension is related to the understanding of all major biological transitions in terms of changes in the type of organization of the systems involved.

Now, if the idea of organism turns out to be crucial to understand the living, we should ask what is its basic organizational structure, its minimal and common set of properties, from the most simple unicellular examples to the more complex ones. In its most elementary general expression, an organism is a collection of parts (molecules, cells, and so on) that put together an integrated whole, according to an arrangement that allows it to *act* in its environment in order to maintain and reproduce itself. Thus, the organization of organisms implies that the component parts and processes of the organized entity are not only responsible for producing each other and the whole, but get actually subjugated under the power of that entity to carry out global, highly coordinated, actions: i.e., to behave like an *agent*.

As we mentioned above, a minimal autonomous organization already involves these two deeply interconnected spheres that define an organism: the functional integration of processes and components making up the system, and the asymmetric interactive loop with the environment, which makes it actually an agent (in Kauffman's 2000, 2003, words: a system «acting on its own behalf»). Similarly to what we said about life at the collective level (which maintains itself because it keeps evolving), at the individual level organisms maintain themselves in so far the underlying biosynthetic machinery keeps running and interacting with the environment; otherwise they simply disintegrate. Living beings are, ultimately, chemical systems that do not stop synthesizing components, and with those components they synthesize some others, build up their cells and organs, repair informational/control devices, or produce the fuel (the type of energy required) to grow, move, capture nutrients and other energy resources, etc. All the functional actions they

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[6] Some of the authors we just mentioned would consider that a theory of self-organization could be enough for the purpose, even if its integration within the standard evolutionary framework remains problematic (Edelman and Denton 2007). Indeed, a lot of processes, shapes or functional patterns that we observe in biological systems (at many different phenomenological levels) reflect self-organizational principles, so their weight should not be underestimated. But, beyond self-organization, the constitution of an organism requires a more cohesive type of organization, as we try to explain below.

perform, inwards and outwards, cycle around that ongoing (self-building, self-repairing and self-reproducing) biochemical intra- and inter-cellular machinery.

Final Remarks

Biological knowledge is not hindered any more by our own difficulties or inability to obtain extensive data from living systems. Rather, the frontier of understanding seems to move away with the continuous accumulation of information in present days. Theoretical and philosophical efforts to define life may contribute to the holistic or synthetic approach necessary to make sense out of that huge amount of information being collected by the different fields and research traditions in biology. Our proposal, on those lines, is that the core of life can be captured by two fundamental constructs: autonomy and open-ended evolution. Although autonomy may initially appear as a high level concept (with too many extra-biological connotations), in its minimal sense ('basic autonomy') it provides just the necessary explanatory power to account for the complex material organization underlying any organism. After all, in the biological domain it is individual organisms that more obviously self-maintain, self-repair and reproduce, adapt and act functionally on their environment. Nevertheless, the wider historical and collective-evolutionary perspective must not be disregarded, or assumed to be of secondary importance. In fact, it is the complementary combination of the two perspectives that offers the adequate solution. A conception of autonomy that comprises both *functional integration* and *agency* is suggested as crucial to develop a theory of evolutionary transitions that may lead to ever more complex organisms, taking into account the increasingly elaborate and indirect relationships established between system and environment. Such an encompassing theoretical framework should also illuminate, in its most elementary version, the precursory steps of life on Earth.

Note Added in Proof Vasas et al. (2010) have recently explored the limits of evolution in self-sustaining autocatalytic networks. Their results support our view that the absence of a reliable system to keep and transmit complexity (i.e. the absence of genetic records) fundamentally constrains the potential to evolve. Nonetheless, self-sustaining, compartmentalized autocatalytic networks (or 'basic autonomous systems' in our terms) still represent the most plausible scenario as the initial bridge between self-organizing and living phenomena.

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